REMARKS

Applicants submit this response to the Office Action of May 6, 2003. As a result of a restriction requirement dated October 1, 2002, the invention has been restricted into six claim groups (I-VI), and further into four sequence groups (A-D), whereby election of one of group I-VI, and one of group A-D was required. Applicants elected group I, directed to nucleic acid vectors, host cells comprising same and methods of expression of the nucleic acid, and group (B) comprising nucleotide sequence SEQ ID NO:4 and amino acid sequence SEQ ID NO:6. As a result, claims 1-6 are pending and claims 7-25 are withdrawn from consideration. Claim 1 is amended to recite the elected sequences, and further amendments are discussed below. The recitation of "95% identity" in claim 1 is supported at least at page 60, lines 7-9 of the specification. No new matter is added.

An Information Disclosure Statement is filed herewith to confirm that the patents and publications intended to be disclosed for the record, and which are cited in the specification, are made of record.

Claims 1-6 are objected to for reciting nonelected subject matter. This has been addressed by amending independent claim 1, from which claims 2-6 depend.

Claims 1-6 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without acquiescing to the ground of rejection, applicants submit that claim 1 as amended is not subject to the specific grounds of objection ("about" language, and "ATP binding site").

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification so as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing, had possession of the claimed invention. Without acquiescing to the ground of rejection, applicants have amended claim 1, from which claims 2-6 depend. The Examiner recommended adding functional language to the rejected claims (Office Action, page 5, lines 8-9), and the amended claims address this issue. The kinase activity of the polypeptide expressed by the claimed nucleic acid molecule is disclosed in the specification at, for example, page 245, first paragraph and page 247,

lines 10-12. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph (enablement). The Examiner states that the specification is enabling for a nucleic acid molecule comprising a polynucleotide sequence encoding SEQ ID NO:6. However, the specification allegedly is not enabling for any nucleic acid molecule at least 90% identical to a sequence encoding SEQ ID NO:6; a sequence that is 50, 100 or 500 contiguous nucleotides of the coding region of SEQ ID NO:4; or any sequence except for at least one amino acid substitution in the encoded amino acid sequence. The Examiner cited the Wands factors (*In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988)).

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (C.A.F.C. 1988). Applicants submit that the amount of experimentation that may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a

particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q.2d at 1407. Thus, Wands supports the conclusion that, in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole may yield negative results does not mandate a finding that the amount of experimentation to achieve a positive result is undue.

Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* Applicants submit that one of ordinary skill in the art can construct a hybridization probe based on the disclosed polynucleotide, SEQ ID NO:6, and use the probe to locate and obtain hybridizing DNA. The polypeptide encoded by the hybridizing DNA would be tested for PAR-1Bα activity (as claimed, kinase activity), and the polynucleotide would be evaluated on the basis of the limitations of the claimed identity with the amino acid sequence of SEQ ID NO:4. If the results of these routine procedures were positive, the polynucleotide sequence would fall within the scope of the claims. Such tests would not constitute "undue" experimentation within the scope of Wands. To determine if a polynucleotide falls within the scope of the claims, the only experimentation required is the performance of transfection and assay procedures. These procedures are routine and would not have to be done repeatedly before a clear result was obtained. Because the inventors and the art provide means for the objective measurement of a polynucleotide falling within the claim scope, this factor is met, for example, by the ability of the polynucleotide to encode a protein capable of blocking the inhibitory activity of mutant Kinase-negative PAR-1 (KN PAR-1). This is described in the specification at pages 246-247.

The Wands court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (8 USPQ2d at 1406.) The court further stated that an "experiment" was not simply the screening of a single hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (8 USPQ2d at 1406).

By analogy, a single experiment in the present art could include obtaining or constructing a polynucleotide, transfecting it into CHO cells that co-express wild-type PAR-1, and determining if Dvl is phosphorylated. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

2. *Amount of direction or guidance provided.* Like the production of monoclonal antibodies, the identification or production of DNA encoding a polypeptide having PAR-1B α activity and falling within the scope of the claims may require some experimentation, but if viewed in the light of Wands, this experimentation is not undue. The present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain DNA that is within the scope of the claims. The Examiner stated that "it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims..." (Page 7, first full paragraph.) Applicants, first, request that the Examiner provide support for this statement about what is and is not routine in this art. Second, the claims do not require a practitioner in this art to "screen for multiple substitutions or multiple modifications." Instead, the screening would entail testing one or more polypeptides for activity as described in the specification, to determine if a given polynucleotide encodes a polypeptide within the scope of the claims. The specification provides clear directions for performing the procedures, and provides cites to published scientific articles for details not mentioned in the specification. Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent application at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8

USPQ 2d at 1404, 1405). The cell lines used in applicants' methods are commercially available, and the application describes the methods, at pages 245-247.

3. *Presence or absence of working examples*. The specification describes transfection of CHO cells using a claimed polynucleotide of the invention, specifically PAR-1B α. (Page 247, lines 10-11.) The co-expression experiment provides an example that is applicable to other claimed polynucleotides (test polynucleotides), which would be co-expressed in the CHO cells along with the mutant (PAR-1 KN) construct. The blocking of inhibitory effects of PAR-1 KN would signal that the test polynucleotide is within the scope of the claims.

These experiments show that it is routine to detect the effect of PAR-1 inhibition. This can be accomplished by transfecting HT1080 cells with an antisense oligonucleotide, lysing the cells after a period of incubation, and analyzing (a) PAR-1 protein content using antibodies, and (b) activity of a reporter gene, specifically a LEF1 reporter. These experiments provide an objective way of measuring PAR-1 activity. The methods are disclosed in the Sun *et al.* publication. These methods are also disclosed in the present patent application at page 247-248, Example 6.

Example 5 of the application, at pages 246-247, describes experiments in which cDNAs for PAR-1 were transfected into Chinese hamster ovary (CHO) cells. In one set of experiments, cDNAs encoding mutant forms of PAR-1, which did not have kinase activity, were transfected into CHO cells. In the absence of the kinase activity, the target of PAR-1 phosphorylation, Dishevelled (Dvl), is not phosphorylated. This result is detected as a reduced amount of a retarded Dvl band. Importantly for the purposes of this invention, if wild-type PAR-1 (capable of phosphorylating Dsl) is co-expressed with the mutant forms of PAR-1 in the CHO cells, the inhibitory activity of the mutant PAR-1 is blocked. This provides a method for determining if a polynucleotide sequence with a given percent homology to SEQ ID NO:6 is capable of functioning as a wild-type PAR-1 sequence, namely, able to encode functional PAR-1 protein. Such experimentation is routine, as it employs known methods and known materials, and needs only the addition of a test polynucleotide to measure objectively whether the polynucleotide falls within the scope of the claims.

4. *Nature of the invention.* The inventors have, for the first time, identified and cloned a human homologue of the *Drosophila* gene referred to as PAR-1. Three human homologues were identified and cloned, and one, the PAR-1Bα form, is under examination in this application. As discussed in a related publication by the inventors, Sun, Tian-Qiang *et al.*, "PAR-1 is a Disheveled-associated kinase and a positive regulator of Wnt signaling," *Nature Cell Biology* 3:628-636, 2001, PAR-1 plays a role in a pathway referred to as the Wnt pathway. Through a series of receptor interactions, Wnt enhances the ability of a protein to antagonize the activity of glycogen synthase kinase 3β. The effect of this pathway, and the associated interactions of the components, is to stabilize the cytosolic protein β-catenin. β-catenin in turn moves to the nucleus, where it combines with a transcription factor to regulate expression of genes. In humans, abnormalities in regulation of the Wnt pathway can cause cancer, as described below. PAR-1 has been shown by the inventors to modulate this Wnt-β-catenin pathway. Thus, it is an important protein from the perspective of its role in normal cell function, and because the Wnt pathway is implicated in cancer, proteins that play a role in this pathway are also implicated in cancer. Functionally, PAR-1 is a serine-threonine kinase.

The inventors designed and performed experiments to determine how cells would react to inhibition of PAR-1. HT1080 cells were chosen because oligonucleotides such as antisense RNA can be delivered to these cells with relative ease, and because HT1080 has a robust transcriptional response to Wnt, allowing the investigator to detect changes in gene expression resulting from disruption of this pathway. (Sun *et al.*, page 632, left column, lines 10-17.) Antisense oligonucleotides capable of specifically binding to PAR-1 reduced PAR-1 messenger RNA (mRNA) by 75-90%, and also reduced PAR-1 protein levels. The inhibition was accompanied by a reduction in Wnt-induced reporter activity. (Sun *et al.*, page 632, left column, lines 17-20). These results showed that (a) it is possible to connect an inhibition of PAR-1 with processes associated with PAR-1 activity, and (b) it is possible to *selectively* inhibit PAR-1 mRNA levels and protein levels. This selective inhibition is achieved using antisense oligonucleotides that specifically recognize and hybridize with PAR-1 sequences of the invention.

The invention relates to human polynucleotides. Methods of synthesizing, isolating, mutating, manipulating, transfecting, and expressing polynucleotides are the basis of the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art.

5. *The state of the prior art.* The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of polynucleotides, specifically hPAR-1 polynucleotides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 USPQ 2d at 1406). Similarly, the methods of transfecting cells, expressing protein, and measuring protein activity are well known, as evidenced by the Sun *et al.* publication and references cited therein.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody was high at the time the application was filed. Importantly, the court also found that *development of skill* in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 USPQ 2d at 1406). By analogy, it would not defeat enablement for one of skill in the art of DNA transfection and expression to learn and become proficient in techniques for practicing the present invention.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when PAR-1Bα is co-expressed in CHO cells with PAR-1 KN, the inhibitory effect of PAR-1 KN would be blocked. The person of skill, testing other polynucleotides as claimed, would predict that the outcome would reflect the ability of the test polynucleotide to encode a functional PAR-1 having kinase activity, and that this would be the only variable affecting the results. Those of skill in this art are acquainted with the need to run appropriate control experiments to rule out unrelated factors as affecting the results.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step might be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. Finally, transfection of a CHO cell and measuring the presence of kinase activity is known, and the Examiner has provided no evidence that the transfection step would be "more difficult or unreliable" (8 USPQ2d at 1406) than for wild-type hPAR-1.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any nucleic aid molecule meeting the limitations of the claims, and test it for activity as described for the previous factors.

In view of the foregoing remarks, applicants submit that the Examiner has not met his burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Espinosa *et al., Cytogenet Cell Genet.* 81:278-282 (1988) as evidenced by Espinosa *et al.,* Genbank Accession No. X97630, October 1998. Without acquiescing to the ground of rejection, applicants submit that the claims as amended are not subject to this ground of rejection.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

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